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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/000,439	SAXON, ANDREW	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,9-14,16-34 and 40-49* is/are pending in the application.

4a) Of the above claim(s) *45-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,9-14,16-34 and 40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 4, 9-14, 16-34, and 40-49 are pending.

2. Claims 45-49 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 1, 4, 9-14, 16-34 and 40-44, drawn to an isolated fusion molecule wherein the autoantigen is myelin basic protein, and a pharmaceutical composition comprising said fusion molecule are being acted upon in this Office Action.

4. In view of the amendment filed 10/2/06, the following rejections remain.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4, 9-14, 16-34 and 40-44 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated fusion molecule comprising hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 2 encoded by SEQ NO: 1 capable of binding to a native IgG inhibitory receptor directly fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting of the amino acid sequence of SEQ ID NO: 13 wherein the fusion molecule is capable of specific binding to a native IgE receptor through a myelin protein specific IgE antibody, (2) the said fusion protein wherein the native IgG inhibitory receptor is a low-affinity FcγRIIb IgG receptor, (3) the said fusion protein wherein said IgE receptor is a high-affinity FcεRI IgE receptor or a low-affinity FcεRII IgE receptor, **does not** reasonably provide enablement for any fusion molecule as set forth in claims 1, 4, 9-14, 16-34 and 40-44 for treatment or "prevention" of any autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims are drawn to any isolate fusion molecule comprising any first polypeptide comprising at least 85% identity to any IgG heavy chain constant region connected directly or indirectly via a polypeptide linker to any second polypeptide autoantigen sequence which comprises at least 90% sequence identity to any "portion" of the amino acid sequence of myelin basic protein (MBP) that are capable of cross-linking any native IgG inhibitory receptor and any native IgE receptor through myelin specific autoantibody IgE for treating and preventing any immune disease, any immune disease such as any autoimmune disease.

The term "portion" as defined in the specification at page 29 is any portion of a polypeptide may range in size from two amino acid residues to the entire amino acid sequence minus one amino acid. The term "at least a portion" encompasses portions as well as the whole of the composition of matter.

The term "high stringent conditions" as defined in the specification at page 24 "*may be* hybridization in 50% formamide, 6x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (PH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (100 µg/ml, 0.5% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 2x SSC (sodium chloride/sodium citrate) and 0.1% SDS at 55OC, followed by a high-stringency wash consisting of 0.2x SSC containing 0.1% SDS at 42°C.

The term "IgG inhibitory receptor" as defined in the specification at page 19 is any member of inhibitory receptor superfamily (IRS), now known or hereafter discover, that is capable of attenuating an FcER-mediated response, regardless of whether it is mediated via IgE acting through a high-affinity IgE receptor, e.g. FcERI, or a low-affinity IgE receptor, or by another mechanism such as an autoantibody to the FcER.

The specification does not teach how to identify other portion ranging from two amino acids to myelin basic protein that has at least 10% amino acids difference in the claimed fusion

protein that retains the activity for the intended use such as treating and preventing autoimmune disease. There is not a single fragment from the smallest to the largest fragment of myelin basic protein fused to any IgG heavy chain constant region shows any biological effect for treating immune disease, any immune disease such as autoimmune disease.

The specification discloses only an isolated fusion molecule comprising a first polypeptide wherein the first polypeptide consisting of a hinge-CH2-CH3 of human IgG1 constant region of SEQ ID NO: 2 encoded by SEQ ID NO: 1 fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting the amino acid sequence of SEQ ID NO: 13, and (2) an isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 1 fused to a human IgE constant region CH2-CH3-CH4 domains of SEQID NO: 7 for inhibiting IgE mediated release of histamine.

The specification does not teach how to make and use all fusion molecule mentioned above for treating, much less for "preventing" any autoimmune disease because of the following reasons. First, the structure such as the amino acid sequence of the fusion molecule is required. Second, there is insufficient guidance as to the structure and the length of the first polypeptide within the fusion protein without the amino acid sequence. The specification does not teach which amino acids within the full-length sequence of all IgG heavy chain constant region are critical and can or cannot be change such as substitution, deletion, addition and combination thereof and whether the resulting IgG heavy chain constant region merely have 85% sequence identity with an IgG heavy chain constant region still binds to which native IgG inhibitory receptor. Further, the term "comprising" is open-ended. It expands the first polypeptide to infinity, such as the full-length sequence of IgG, not just the Fc fragment. In addition to the problem mentioned above, the term "at least 85% identity" means there is at least 15% difference. Without knowing the length of the first polypeptide, it is not clear how one skill in the art to come up with the sequence identity that based on the total number of amino acids in the first polypeptide. Even if the length of the sequence is recited in the claim, there is insufficient guidance as to which amino acids within the IgG heavy chain constant region to be substituted, deleted, added and/or combination thereof such that the resulting IgG heavy chain constant region still binds to which native IgG inhibitory receptor. It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein.

Stryer et al, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo et al, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Tao et al teach the ability to activate complement and to bind to FcγRI, both of which are dependent on the CH2 domain of IgG heavy chain (see entire document, page 2599, col. 2, second full paragraph, in particular). Tao et al teach even a single amino acid substitution in the CH2 domain of human IgGs from Asn-297 to His for IgG1 or Lys for IgG3 affected the structure and functional properties of the human IgGs. The resulting aglycosylated IgGs lose the ability to activate complement (C) (see page 2598, Fig 2, page 2599, col. 2, third paragraph, in particular), lost the ability to bind FcγRI (see page 2600, col. 1, first paragraph, in particular) and shortening the serum half-life of the aglycosylated IgG3 (see abstract, in particular).

Third, with regard to the second polypeptide autoantigen in the fusion protein, there is insufficient guidance as to the structure and length of the second polypeptide autoantigen within the fusion protein without the amino acid sequence. Specifically, there is insufficient guidance as to which "portion" of the myelin basic protein in the second polypeptide autoantigen is part of the fusion molecule. Given the "portion" of autoantigen sequence can be any length, it is not clear how one skill in the art be able to determine the sequence identity given the length is not finite. It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein.

McDevitt et al teach administering autoantigen comprising a "portion" of an autoantigen such as epitopes 206-220, 221-235 and 286-300 of GAD to NOD mice resulted in the prompt onset of an immediate hypersensitivity and death of animal (page 14628, col. 2, last paragraph, in particular). Without guidance as to the portion or epitope of autoantigen to be fused to the any IgG heavy chain constant region, it is unpredictable which fusion molecule is effective for treating any autoimmune disease, much less for "preventing" all autoimmune diseases (claim 44).

Fourth, with regard to percentage of sequence identity (claims 1 and 18-21), in addition to the lack sequence for the first and second polypeptides in the fusion molecule mentioned above, there is insufficient guidance as to which amino acids within the full-length polypeptide

can be modified and yet maintain its function. It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even a single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Mikayama *et al*, of record, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama et al further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that amino acid sequence determines the function of the polypeptide or protein. However, the predictability of which changes can be tolerated in an amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance such as which amino acids within the full-length polypeptide are tolerant of modification and which amino acid residues are conserved or less tolerant to modification in which the product's structure relates to its functional usefulness. The use of "percent" in conjunction with any of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Because applicants have not disclosed the specific condition used to score sequence identity while using any computer program, it is unpredictable to determine which amino acid sequences of autoantigen in the claimed fusion molecule will have at least about 90% identity to which "portion" of myelin basic protein fused to which first polypeptide will have at least 85% sequence identity to which IgG heavy chain is effective for treating multiple sclerosis. Even if the autoantigen is "comprises at the amino acid sequence of SEQ ID NO: 13 (claim 10), SEQ ID NO: 13 is an epitope or fragment of myelin basic protein. Further, the term "comprises" expands the fragment to include additional amino acids at either or both ends of SEQ ID NO: 3. There is insufficient guidance as to which amino acids to be added.

Warrant et al (abstract) teach administering myelin basic protein fragment such as MBP35-58 to multiple sclerosis patient had to effect on the anti-MBP level. However, only

administering MBP 75-95 resulted in a significant in the autoantibodies over a period of one month (see abstract, in particular). The specification as filed does not teach which amino acids to be added and whether any fragment of myelin basic protein when fused to any first polypeptide comprising at least 85% identity is effective for treating autoimmune multiple sclerosis. Likewise, the same reasons apply to claims 18-21.

Attwood et al teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document).

Fifth, with regard to claims 24, the term "comprises" is open-ended. It extends the hinge, CH2 and CH3 domains of a native human IgG1 heavy chain constant region to include the light chain such as Fab fragment of the full-length human antibody.

Sixth, with regard to the first polypeptide sequence "comprises an amino acid sequence" encoded by any nucleic acid hybridizing under stringent conditions to which "portion" of the complement of the IgG heavy chain constant region nucleotide of SEQ ID NO: 1 (claim 25), the nucleic acid that hybridizes to the complement of SEQ ID NO: 1 could be an oligonucleotide, which does not encodes the whole IgG heavy chain constant region, let alone binding to a native IgG inhibitory receptor. There is insufficient guidance as to the structure of the oligonucleotide that encodes which portion of the complement of IgG heavy chain constant region that binds native IgG native receptor in the claimed fusion molecule. Further, there is insufficient guidance as to the "hybridization stringent conditions". Further, there is insufficient guidance as to which "portion" of the complement of the IgG heavy chain that the nucleic acid hybridize to. The state of the prior art as exemplified by Wallace *et al,* of record, is such that determining the specificity of the oligo and hybridization conditions are empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. The claim as written is improper for an isolated fusion molecule.

Skolnick et al, PTO 1449, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Given the unlimited number of undisclosed fusion molecules, there is insufficient in vivo working example demonstrating that any fusion molecules are effective for treating all autoimmune diseases. It has been well known to those skilled in the art at the time the invention

was made that minor structural differences among structurally related compounds or compositions could result in substantially different biological or pharmacological activities. Even if the fusion molecule is limited to human Fc fused to the myelin basic protein, there is a lack of in vivo working example demonstrating that the fusion is effective for treating multiple sclerosis, let alone for "the prevention of any immune disease" or autoimmune diseases.

Seventh, with regard to pharmaceutical composition (claims 40-41) and article of manufacture (claims 42-44) comprising any fusion molecule mentioned above for the "treatment" or "prevention" of any immune disease, any immune disease such as any autoimmune disease, given the structure of the fusion molecule is not enable, it follows that any pharmaceutical composition or any article of manufacture comprising the undisclosed fusion molecule are not enabled. Further, a pharmaceutical composition in the absence of in vivo is unpredictable for the following reasons: (1) the fusion molecule may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the fusion molecule may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the fusion molecule unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Blanas et al (of record, Science 274: 1707-1709, Dec 1996; PTO 1449) teach treating autoimmune rheumatoid arthritis and multiple sclerosis by oral administering autoantigen could lead to onset of autoimmune diabetes (see abstract, in particular).

Couzin et al, of record, teach that finding the tell tale antibodies doesn't guarantee that autoimmune diabetes sill strike (See page 1863, Science 300: 1862-65, 2003). Couzin *et al* teach that three major prevention trials have failed to stop autoimmune disorder such as type I diabetes (See entire document).

Davidson *et al,* PTO 1449, teach that two recent phase I clinical trial for treatment of multiple sclerosis by administering myelin basic protein peptide resulted in exacerbations of multiple sclerosis (See page 346, col. 2, in particular). In the absence of guidance and vivo working example, it is unpredictable which pharmaceutical composition comprising the undisclosed fusion molecule is useful for treating multiple sclerosis, let alone for "preventing" any autoimmune disease. The specification does not teach any assays that is useful for screening

variants and is predictive of success in vivo. Given the unlimited number of fusion molecule, it is unpredictable which undisclosed fusion protein is effective for treating for treating any immune disease, any autoimmune disease such as multiple sclerosis, let alone "preventing" any immune disease, any immune disease such as any autoimmune disease in the absence of working example (claim 44).

Since the structures of the first and second polypeptides of the claimed fusion molecule mentioned above are not enabled, it follows that any first polypeptide and any second polypeptide connected through any linker (claim 26), any linker such as polypeptide linker (claims 27-28) are not enabled. It also follows that any undisclosed fusion protein comprising at least one amino terminal ubiquination target motif (claim 29), any proteosome proteolysis signal (claims 30-31) or any endopeptidase recognition motif (claims 32-34) are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 10/2/06 have been fully considered but are not found persuasive.

Applicant's position is that the present invention concerns certain novel fusion molecules that are capable of cross-linking a native IgG inhibitory receptor with a native IgE receptor. The fusion molecules comprise a sequence comprising at least 85% identity to IgG heavy chain sequence linked to a polypeptide autoantigen sequence which comprises at least 90% identity to at least a portion of myelin basic protein and is capable of specifically binding to an IgE class immunoglobulin. The purpose of these molecules is to allow the myelin basic peptide to function as an immunogen while any fusion peptides that reacted with IgE loaded mast cells would not trigger an adverse reaction. While the therapeutic strategy and the construct underlying the present invention is both novel and unobvious, the fusion molecules themselves have a relatively simple structure, and can be made and -tested by standard techniques that were well known in the

art at the time of making the present invention. Furthermore, at the time the present invention was made, there was a lot of information known in the art about the interaction of IgG inhibitory receptors and IgE receptors with antibody constant regions, which provides valuable information for the construction of the fusion molecules of the present invention. Accordingly, although unpredictability in the field of recombinant DNA technology is generally viewed as relatively high, the unpredictability in the particular field to which the present invention pertains is of lesser degree. Example 2 of the specification provides the method for generating the fusion molecules.

In contrast to applicants' assertion that the structure of the claimed fusion molecules themselves have a relatively simple structure and can be made and tested by standard techniques that were well known in the art at the time of making the present invention, the specification as filed does not teach how to make any isolated fusion molecule comprising at least 85% identity with which IgG heavy chain constant region capable of binding to which native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least a portion of the amino acid sequence of myelin basic protein (MBP) and capable of specific binding to an IgE class immunoglobulin. This is because of the following reasons. First of all, the specification does not teach which "portion" of the amino acid sequence of myelin basic protein binds to IgE immunoglobulin. Second, given the lack of guidance as to the "portion" of the amino acid sequence of myelin basic protein binds IgE, there is insufficient guidance as how to go about determining the percent identity such as at least 90% sequence to the undisclosed portion of myelin protein. Even assuming the myelin basic protein is the full-length sequence, a sequence with 90% identity means there is at least 10% difference. There is a lack of guidance as to the structure of myelin basic protein having at least 10% difference still binds to IgE class immunoglobulin, let alone fused to any first polypeptide comprising at least 85% identity to any IgG heavy chain constant region. The specification does not teach which amino acids within the full-length sequence of myelin basic protein to be substituted, deleted, added or combination thereof such that the undisclosed portion of myelin basic protein having at least 90% sequence identity still binds to IgE. Further, the term "comprising" is open-ended. It expands the "portion" of the undisclosed amino acid sequence of myelin basic protein to be included additional amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added. With regard to the IgG heavy chain constant region of the claimed fusion protein, the specification does not teach which amino acids within any IgG heavy chain constant region to be substituted, deleted, added,

and combination thereof such that the IgG heavy chain still maintains its structure, and still binds to which native IgG inhibitory receptor. Given the lack of guidance as to the structure of the fusion protein as a whole, the specification merely extends an invitation to one skill in the art to come up with the structure of claimed fusion protein, let alone for use in treating autoimmune disease.

At page 12 of the argument, applicant points out that the specification describes methods for the determination of percent identity between two amino acid sequences (see Specification, page 23, lines 4 - 13). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Also, one of ordinary skill in the art will recognize that the prior art provides numerous sources that describe IgG Fc sequences highly homologous to the Fc sequences of SEQ ID NO: 3 (see, the Specification at page 26, line 19 - page 27, line 6).

Applicant's argument at page 12 of the response has been fully considered but is not deemed persuasive. The claims are drawn to any isolated fusion molecule comprising any first polypeptide sequence comprising at least 85% identity with any IgG heavy chain constant region directly and functionally connected to any second polypeptide autoantigen sequence comprising at least 90% sequence identity to at least any portion of the amino acid sequence of myelin basic protein and capable of specific binding to an IgE class immunoglobulin. The claims are not drawn to a fusion protein comprising at least 85% identity to SEQ ID NO: 3 as argued.

At page 13-15 of the argument, applicant argues that it is well known in the art to do site-directed mutagenesis, or alanine-scanning mutagenesis and then the resulting mutant molecules are tested for biological activity.

Applicant's argument has been fully considered but is not deemed persuasive. Testing or screening for activity, once the fusion polypeptide is made, is not sufficient to provide enablement for how to make without guidance as to the structure, i.e., amino acid sequence of the claimed fusion protein, let alone how to treat any autoimmune disease as disclosed in the specification, see pages 6-7 of specification in the absence of any in vivo working example.

At page 16 of the response, applicant argues that the IgG sequence is well known and the MBP sequence is well known. This application is not directed to identifying a function of a protein based on sequence similarity. The compound is a fusion protein. A full length antibody,

the light chain is a separate polypeptide. Second, the present application describes, by way of example, additional non-essential but advantages amino acid sequences and other elements that fine use with the first and second polypeptide of the fusion molecules.

Applicant's argument at page 16 of the response has been fully considered but is not deemed persuasive. As explained in the previous Office Action, the use of "percent" in conjunction with any of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Because applicants have not disclosed the specific condition used to score sequence identity while using any computer program, it is unpredictable which amino acid sequences of autoantigen in the claimed fusion molecule will have at least about 90% identity to which "portion" of myelin basic protein, especially the length of the "portion" is not even a fixed number, fused to which first polypeptide will have at least 85% sequence identity to which IgG heavy chain is effective for treating multiple sclerosis. Even if the autoantigen "comprises at the amino acid sequence of SEQ ID NO: 13 (claim 10), SEQ ID NO: 13 is an epitope or fragment of myelin basic protein. The term "comprises" expands the fragment to include additional amino acids at either or both ends of SEQ ID NO: 3. There is insufficient guidance as to which amino acids to be added.

The specification discloses only an isolated fusion molecule comprising a first polypeptide wherein the first polypeptide consisting of a hinge-CH2-CH3 of *human* IgG1 constant region of SEQ ID NO: 2 encoded by SEQ ID NO: 1 that is capable of binding to a native IgG inhibitory receptor fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting the amino acid sequence of SEQ ID NO: 13, and (2) an isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 1 fused to a human IgE constant region CH2-CH3-CH4 domains of SEQID NO: 7 for inhibiting IgE mediated release of histamine. The specification does not teach any other fusion protein as broadly as claimed for the reasons of record. The term "comprising" expands the hinge-CH2-CH3 domain of any IgG to include the CH1 domain of the heavy chain. Further, the specification disclose only IgG constant region from human. The claims are drawn to any IgG constant having at least 85% sequence identity to any IgG constant fused to any myelin basic

protein comprising at least 90% identity to any portion of the amino acid sequence of myelin basic protein.

At pages 17-18 of the response, applicant argues that claim 1 and all claims dependent on claim 1, including claim 25, contain the functional limitation that the IgG domain has the ability to bind to the native IgG inhibitory receptor and that the myelin basic protein (MBP) is capable of specific binding to an IgE class immunoglobulin. The term "portion" does not result in an infinite number of fusion molecules with unpredictable activities. The identification of fusion molecules that meet the limitation of the claims is routine and does not require undue experimentation. At the footnote of page 18, applicant presumes that eh Examiner intended to cite Davidson et al, (2001) New England J of Med 345(5): 340-350, Eds. MacKay & Rosen rather than MacKay et al.

Applicant's argument at pages 17-18 of the response has been fully considered but is not deemed persuasive. Screening for activity, once the fusion polypeptide is made, is not sufficient to provide enablement for how to make without guidance as to the structure, i.e., amino acid sequence of the claimed fusion protein, let alone how to treat any autoimmune disease as disclosed in the specification, see pages 6-7 of specification in the absence of any in vivo working example. Until the structure of the fusion protein is adequately described, one of skill in the art cannot make, much less for treating any autoimmune disease such as multiple sclerosis. With respect to the argument that the specification discloses the epitope or portion of MBP, none of the claims recite the specific epitope as argued, let alone a fusion protein comprising at least 90% sequence to any portion of MBP fused to any first polypeptide comprising at least 85% sequence identity with any IgG heavy chain constant region.

With respect to applicant's presumption that that the Examiner intended to cite Davidson et al, (2001) New England J of Med 345(5): 340-350, Eds. MacKay & Rosen rather than MacKay et al is corrected. The Examiner apology for any confusion that may have cause applicant.

At page 19 of the response, applicant argues that Blanks indicates that oral administration of ovalbumin autoantigen in mice was found to induce a cytotoxic T lymphocyte response that could lead to the onset of autoimmune diabetes. Blanas does not discuss the MBP peptide or multiple sclerosis. Applicant's construct comprises the heavy chain constant region of the IgG fused to the MBP peptide. The fusion molecule acts to inhibit the autoallergic reaction. Blanas

does not discuss the administration of a fusion molecule, let alone a fusion molecule comprising an autoantigen fused to the IgG heavy chain constant region, as claimed. Couzin et al. (2003) is an article reviewing various clinical tests for the treatment and prevention of type I diabetes. Couzin does not discuss the MBP peptide, use of a fusion polypeptide or multiple sclerosis. For the reasons set forth for Blanas, the findings of Couzin et al. cannot be applied properly to the currently claimed invention. Furthermore, the legal standard sufficient to establish enablement of a compound is in vitro or in vivo animal model tests. In any case, human clinical trials are not required.

Applicant's argument at page 19 of the response has been fully considered but is not deemed persuasive. There is no evidence in the specification as filed regarding the claimed fusion polypeptide is effective for treating autoimmune disease such as multiple sclerosis. Both references were cited to establish the state of the art, which is that treating autoimmune disease is not predictable. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance as to the structure of fusion protein in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

At page 20 of the response, applicant argues that Davidson et al., states that two recent phase I clinical trials for treatment of multiple sclerosis by administering altered peptide ligands derived from MBP resulted in either hypersensitivity reactions or exacerbations of multiple sclerosis. (page 346) First, Davidson does not indicate that the altered peptide ligands derived from MBP are functionally attached to the IgG heavy chain constant regions. The purpose of the IgG Fc regions is to prevent the hypersensitivity reaction seen with the peptides as taught by MacKay. Accordingly, Davidson does not teach that the claimed invention will not work. Furthermore, the legal standard sufficient to establish enablement of a compound is in vitro or in vivo animal model tests. In any Case, human clinical trials are not required. McDevitt, allegedly indicates that administration of GAD autoantigen epitopes in NOD mice was found to induce immediate hypersensitivity that could lead to death. Applicant's fusion molecules comprise the heavy chain constant region of the IgG fused to the MBP peptide. The fusion molecule acts to inhibit the autoallergic reaction. McDevitt does not discuss the administration of a fusion

molecule, let alone a fusion molecule comprising an autoantigen fused to the IgG heavy chain constant region, as claimed. Accordingly, the findings of McDevitt cannot be applied to the currently claimed invention. Applicant previously enclosed later published papers which show that fusion molecules comprising an IgG constant region linked to an IgE constant region successfully reduces histamine release in animals. Clearly such compounds are not inactivated as suggested by the Examiner. Clearly these types of fusion molecules can be successfully administered to animals (Zhu et al, (2002()) Nature Medicine 8(5): 518-521; Kepley et al (2003) clinical Immunology 108: 89-94.

Applicant's argument at pages 19 of the response has been fully considered but is not deemed persuasive. Both Davidson et al and McDevitt are cited to establish the state of the art, which is that treating autoimmune disease is not predictable in the absence of in vivo working example. Davidson et al teaches that two recent phase I clinical trials for treatment of multiple sclerosis by administering altered peptide ligands derived from MBP resulted in either hypersensitivity reactions or exacerbations of multiple sclerosis. Similarly McDevitt indicates that administration of GAD autoantigen epitopes to NOD mice was found to induce immediate hypersensitivity that could lead to death. Given the lack of in vivo working example, it is unpredictable whether the claimed fusion protein could treat autoimmune multiple sclerosis as intended.

With respect to fusion molecules can be successfully administered to animals as taught by Zhu et al (Nature Medicine 8(5): 518-521,2002; PTO 1449), Zhu et al teach a fusion protein comprising Fcγ-Fcε for inhibiting IgE mediated passive cutaneous anaphylaxis in transgenic mice expressing human FcεRIα. Zhu et al does not teach a fusion protein comprising an IgG constant region fused to myelin basic protein or fragment thereof. There is no disclosure of the fusion protein as taught by Zhu et al could treat autoimmune multiple sclerosis. In fact, the transgenic mouse as taught by Zhu et al is not the appropriate model for multiple sclerosis.

With respect to fusion molecules can be successfully administered to animals as taught by Kepley et al (Clinical Immunology 108: 89-94, 2003; PTO 1449), Kepley et al teach a fusion protein comprising Fc domain from human Ig1 fused to Fc domain of IgE (GE2) for inhibiting IL-16 production from human langerhans-like dendritic cells expressing the FcεRI. The reference postulates that inhibition of IL-16 production using the fusion molecule may inhibit atopic dermatitis and beneficial in the treatment of allergic inflammation, especially in atopic eczema/dermatitis, allergic rhinitis and asthma, see page 93, col. 1 in particular). However,

Kepley et al does not teach a fusion protein comprising an IgG constant region fused to myelin basic protein or fragment thereof, let alone for treating autoimmune multiple sclerosis.

7. Claims 1, 4, 9-14, 16-34 and 40-44 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any and all fusion molecule as set forth in claims 1, 4, 9-14, 16-34 and 40-44 for treatment or "prevention" of any autoimmune disease.

The specification discloses only an isolated fusion molecule comprising a first polypeptide wherein the first polypeptide consisting of a hinge-CH2-CH3 of human IgG1 constant region of SEQ ID NO: 2 encoded by SEQ ID NO: 1 fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting the amino acid sequence of SEQ ID NO: 13, and (2) an isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 1 fused to a human IgE constant region CH2-CH3-CH4 domains of SEQID NO: 7 for inhibiting IgE mediated release of histamine. The intended use of the claimed fusion protein is to treat autoimmune disease multiple sclerosis, see pages 6-7 of the specification.

With the exception of the specific fusion molecule mentioned above, there is insufficient written description about the structure associated with function of any and all fusion molecules mentioned above without the amino acid sequence. Further, there is inadequate written description about the structure of the first polypeptide in the fusion protein "comprising at least 85% identity" with which IgG heavy chain constant region. The term "comprises" is open-ended. It expands the IgG heavy chain constant region to include the CH1 domain or the whole IgG. In addition, the term "at least 85% identity" means there is at least 15% difference. Not only the length of the first polypeptide is not adequately described, there is inadequate written description about which amino acids within the undisclosed constant region of IgG to be substituted, deleted, added and/or combination thereof such that the first polypeptide of the fusion molecule still binds to the native IgG inhibitory receptor. The same reasoning apply to the first polypeptide as set forth in claim 18-21. Likewise, term "comprises" in claims 22-24 expands the first polypeptide sequence (immunoglobulin Fc region) in the fusion molecule to include additional amino acids at

either or both ends in addition to part of the CH2, CH3 and hinge region to include CH1 fragment.

With regard to the second polypeptide of the claimed isolated fusion molecule, the same reasons apply. There is insufficient written description about the "portion" of the amino acid sequence of myelin basic protein (MBP) that is part of the fusion molecule without the amino acid sequence. Further, the term "comprising" is open-ended. There is inadequate disclosure about which amino acids within the portion to be added, deleted, substituted and combination thereof such that the autoantigen comprising at least 10% difference still be able to bind to any native "IgE receptor" through which third polypeptide sequence, especially the third polypeptide is any immunoglobulin instead of IgE class antibody.

With regard to claim 9, there is inadequate written description about the "portion" of myelin basic protein without the amino acid sequence. Further, the term "comprises" is open-ended. It expands the undisclosed "portion" of the myelin basic protein to include additional amino acids at either or both ends. There is insufficient disclosure about which amino acids to be added, much less for the function of the said portion in the claimed fusion protein.

With regard to claim 10, even the autoantigen sequence in the fusion protein comprises the amino acid sequence of SEQ ID NO: 13, SEQ ID NO: 13 is a fragment or an epitope of myelin basic protein. Again, the term "comprises" is open-ended. It expands SEQ ID NO: 13 to include additional amino acids at either or both ends. There is insufficient disclosure about which amino acids to be added to the autoantigen in the fusion protein.

With regard to claims 18-21, in addition to the problem with the second polypeptide mentioned above, the term "at least 85%, 90%, 95%, 98% identity" to SEQ ID NO: 3 means there is at least 15%, 10%, 5%, 2% sequence difference to SEQ ID NO: 3 in the claimed fusion protein. There is inadequate written description about which amino acids within SEQ ID NO: 3 of the first polypeptide in the claimed fusion protein should or should not be change.

With regard to claims 22-24, in addition to the problem with the second polypeptide mentioned above, the term "comprises" expands the CH2-CH3 domains of a human IgG1 constant region to include the hinge, the CH1 domain or the Fab fragment in the claimed fusion protein. None of the fusion protein in the specification as filed includes CH1 domain or the Fab domain.

With regard to claim 25, in addition to the problem with the second polypeptide mentioned above, there is also inadequate written description about the nucleic acid sequence that

"hybridizes" to which "portion" of the complement of the IgG heavy chain constant region of SEQ ID NO: 1, and under which "stringent hybridization conditions". The nucleic acid that hybridizes to the complement of SEQ ID NO: 1 could be any oligonucleotide, which does not encodes the whole IgG heavy chain constant region or the specific Fc domain, let alone encoding a polypeptide in the fusion protein that binds to a native IgG inhibitory receptor. Thus the structure of the oligonucleotide that encodes which portion of the complement of IgG heavy chain constant region that binds native IgG native receptor in the claimed fusion molecule is not adequately described. Further, claim 25 as written is improper for an isolated fusion molecule.

Adequate written description requires more than a mere statement that it is part of the invention. The amino acid sequence itself for the fusion molecule is required. Until the amino acid sequences of the first, and second polypeptides in the fusion protein have been described, the fusion molecule comprising the first and second polypeptide is not adequately described. Since the fusion molecule is not adequately described, it follows that any pharmaceutical composition and article of manufacture comprising any undisclosed fusion molecules are not adequately described.

Finally, the specification discloses only three fusion molecules wherein the fusion molecule comprises a hinge-CH2-CH3 from only human IgG1 constant region consisting of SEQ ID NO: 2 fused to only myelin basic protein comprising SEQ ID NO: 12 (full length) or a peptide from myelin basic protein consisting of SEQ ID NO: 13, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of fusion molecule to describe the genus of fusion molecule for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant's arguments filed 10/2/06 have been fully considered but are not found persuasive. At pages 21-22 of the response, applicant argues that it is not necessary to provide the amino acid sequence in the specification where the sequence is known in the art. The isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO:I fused to a human IgE constant region CH2-CH3-CH4 domains of SED ID NO:7 for inhibiting IgE mediated release of histamine is not part of the claimed fusion molecule. The specification

describes multiple fusion molecules. For example, the Specification describes the construction of chimeric fusion molecules, see Example 2, pages 180-183. The Specification also describes fusion molecules where the first and second polypeptide sequences of the fusion molecule are connected by use of linkers (see Specification page 27, lines 4-15). Also, the fusion molecules may contain post translational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation or prenylation (as described in the Specification at page 21, line 4 - 24). The Specification describes advantageous fusion molecule variants (page 21, line 25 - page 23, line 3), where the variants have improved affinity for their respective IgG or IgE receptors (Specification, page 34, line 24 - page 35, line 25). The Specification describes fusion molecules comprising multiple copies of IgG and autoantigen (page 54, lines 18-21). Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 63, lines 20-22), and peptide sequence tags to facilitate fusion molecule purification the fusion molecules (page 63, line 32 to page 64, line 3) are also described.

Applicant's argument at pages 21-23 of the response has been fully considered but is not deemed persuasive. Adequate written description requires more than a mere statement that it is part of the invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed fusion molecule and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The amino acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. The Court further elaborated that generic statements are not an

adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

In the instant case, the specification fails to describe the structure of any fusion molecule comprising any first polypeptide sequence comprising at least 85% identity with any IgG heavy chain constant region capable of binding to which native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen sequence comprising at least 90% sequence identity to which portion of the amino acid sequence of myelin basic protein (MBP) and capable of binding to an IgE class immunoglobulin for treating autoimmune disease such as multiple sclerosis. The specification describes only three fusion molecules wherein the fusion molecule comprises a hinge-CH2-CH3 from only human IgG1 constant region consisting of SEQ ID NO: 2 fused to only myelin basic protein comprising SEQ ID NO: 12 (full length) or a peptide from myelin basic protein consisting of SEQ ID NO: 13, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of fusion molecule to describe the genus of fusion molecule for the claimed method.

With respect to the argument that example 2 disclosed at pages 80-83, the specification describes construction of two human fusion polypeptide comprising the hinge-CH2-CH3 portion of the IgG1 constant region, as provided in SEQ ID NO: 1 fused to a full length myelin-basic-protein (MBP) amino acid sequence (as provided in SEQ ID NO: 12), while an alternative version of the fusion polypeptide comprises a portion of MBP containing essentially the minimal, immunodominant autoimmune epitope consisting of the amino acid sequence of SEQ ID NO: 13 fused to the hinge-CH2-CH3 portion of the IgG1 constant region, as provided in SEQ ID NO: 1. The specification has not described any other first polypeptide that is at least 85% identical to any IgG heavy chain constant and still binds to which native IgG inhibitory receptor, let alone fused to any second polypeptide comprising at least 90% sequence identity to at least any portion of myelin basic protein. The specification does not adequately describe which amino acids within the full length IgG heavy chain constant region to be substituted, deleted, added and/or combination thereof such that the fusion protein comprising the modified IgG heavy chain having at least 15% difference still binds to which native IgG inhibitory receptor. The specification does

not adequately describe which portion of myelin basic protein other than SEQ ID NO: 13 to be substituted, deleted, added, and combination thereof such that modified second polypeptide comprising at least 90% identity still binds to IgE class of immunoglobulin when fused to a first polypeptide first polypeptide that is at least 85% identical to any IgG heavy chain constant and still binds to which native IgG inhibitory receptor, in turn, the fusion molecule is effective for treating multiple sclerosis.

With respect to the argument that the specification at page 55, lines 15-25 provides which amino acids are necessary for receptor binding, it is noted that specification at page 55 mere extends an invitation to one skill in the art to test for receptor using any known assay method, such as competitive binding assays, direct and indirect sandwich assays. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

At page 25 of the response, applicant argues that with regard to claim 22-24, none of the fusion proteins in the specification requires the CH1 domain or the Fab domain.

Applicant's arguments have been fully considered but are not found persuasive. The term "comprises" is open-ended. It expands the CH2-CH3 domains of a human IgG1 constant region to include additional amino acids at either or both ends. There is inadequately written description as to what is being included in the claimed fusion molecule.

At page 26 of the response, applicant argues that with regard to claim 25 depends from claim 1 and modifies the polypeptide sequence comprising at least 85% identity with an IgG heavy chain constant region such that the polypeptide must also be encoded by a nucleic acid which hybridizes to at least a portion of the complement of SEQ ID NO: 1.

Applicant's argument at pages 26 of the response has been fully considered but is not deemed persuasive. The hybridization conditions recited in claim 25 needs to be determined empirically. The specification at page 23 discloses the parameters for stringent conditions vary and depend on a number of factors, such as sequence dependent and will be different with different environmental parameters (e.g., salt concentrations, and presence of organics). Generally, stringent conditions are selected to be about 5°C to 20°C lower than the thermal melting point (T) for the specific nucleic acid sequence at a defined ionic strength and pH. Preferably, stringent conditions are about 5°C to 10°C lower than the thermal melting point for a

specific nucleic acid bound to a perfectly complementary nucleic acid. The Tm is the temperature (under defined ionic strength and pH) at which 50% of a nucleic acid (e.g., tag nucleic acid) hybridizes to a perfectly matched probe. "Stringent" wash conditions are ordinarily determined empirically for hybridization of each set of tags to a corresponding probe array. Given the broad range of temperature, salt conditions, the sequence structure, the specification has not adequately described the specific hybridization stringent conditions for the specific nucleotide of SEQ ID NO: 1, let alone the structure of the nucleic acid sequence encoding the first polypeptide in the claimed fusion molecule.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 1, 4, 9-14, 16, 22-28, and 40-41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,116,964 (May 1992; PTO 892) in view of US Pat No 5,858,980 (Jan 1999; PTO 892).

The '964 patent teaches an isolated fusion molecule comprising a first polypeptide such as the constant domain of the IgG heavy chain or the Fc portion of human IgG1, IgG2, IgG3, IgG4 which obviously capable of binding to its native IgG inhibitory receptor such as FcγRIIb IgG receptor fused to a second polypeptide autoantigen sequence such as myelin-associated glycoprotein (MAG) or a portion thereof (see abstract, col. 1, line 34, col. 7, line 45, col. 10, lines 10-15, col. 14, lines 65-67, col. 15, lines 4-17, claims 5 and 7, in particular). The reference full-

length autoantigen myelin-associated glycoprotein (MAG) comprises at least one autoantigenic epitope. The reference autoantigen myelin-associated glycoprotein (MAG) in the reference fusion molecule obviously is capable of binding to IgE autoantibodies that are specific for myelin-associated glycoprotein (MAG) when administered to a human subject, in turn, the myelin-associated glycoprotein (MAG) specific IgE autoantibodies are capable of binding to its native IgE receptors such as FcεRI IgE receptor and FcεRII IgE receptor. The '964 patent teaches the fusion protein wherein the Fc constant retain at least functionally active hinge, CH2, and CH3 domains of an immunoglobulin heavy chain (see col. 10, lines 10-25, in particular). The reference IgG heavy chain constant region in the fusion molecule has at least 98% sequence identity to the claimed human IgG Fc of SEQ ID NO: 2 (see reference SEQ ID NO: 7, in particular). The advantage of Fc improves the in vivo plasma half-life of the fusion molecule (see col. 15, lines 19-20, in particular). The '964 patent teaches a pharmaceutical composition comprising the reference fusion molecule and pharmaceutical acceptable ingredient such as calcium non-phosphate buffer and/or cofactor (see col. 31, lines 4-10, in particular). The '964 patent further teaches the fusion molecule wherein the first and second polypeptide are functionally connected through a polypeptide linkers such lysine residues, as well as other amino, amino, carboxyl, sulfhydryl, hydroxyl or other hydrophilic groups (see col. 23, lines 40-44, in particular). The '964 patent further teaches the reference fusion molecule includes a signal sequence at the N-terminus of hybrid molecule (see col. 26, lines 24-29, in particular), and a secretory leader recognized by the host cells (see col. 26, lines 32-56, in particular). Claim 25 is included in this rejection because the recitation of nucleic acid hybridizing under stringent conditions to at least a portion of the complement of the IgG heavy chain constant region of claimed human IgG Fc of SEQ ID NO: 1 would obviously include the reference human IgG Fc.

The claimed invention as recited in claim 1 differs from the teachings of the reference only in that the fusion molecule wherein the autoantigen sequence is at least 90% identity to at least a portion of the amino acid sequence of myelin basic protein (MBP) instead of myelin-associated glycoprotein (MAG).

The claimed invention as recited in claim 9 differs from the teachings of the reference only in that the fusion molecule wherein the autoantigen sequence present in the fusion molecule comprises at least a portion of the amino acid sequence of myelin basic protein instead of myelin-associated glycoprotein (MAG).

The '980 patent teaches autoantigen such as human myelin basic protein (MBP) and various fragments of MBP such as SEQ ID NO: 18-23, and 16 (see claims of '980 patent, in particular). The reference MBP peptide ENPVVHFFKNIVTPRTP of SEQ ID NO: 18 is 100% identical to the claimed peptide of SEQ ID NO: 13. The '980 patent teaches a pharmaceutical composition comprising protein incorporating immuno dominant epitopes of the reference peptides and pharmaceutical acceptable carrier for administration to patients suffering from multiple sclerosis (see col. 3, lines 45-67, col. 11, lines 20-35 in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the myelin-associated glycoprotein (MAG) in the IgG heavy chain constant fusion molecule as taught by the '964 patent for the myelin basic protein (MBP) that is 100% identical to at least a portion of the amino acid sequence of myelin basic protein (MBP) as taught by the '980 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the Fc improves the in vivo plasma half-life of the fusion molecule as taught by the' 964 patent (see col. 15, lines 19-20, in particular). The '980 patent teaches protein incorporating immuno dominant epitopes of the reference peptides is useful as a pharmaceutical composition for treating patients suffering from multiple sclerosis (see col. 3, lines 45-67, col. 11, lines 20-35 in particular). Claim 28 is included in this rejection because it is within the purview of one ordinary skill in the molecular biology art to use any linker sequence consists of about 5 to about 25 amino acid residues without undue experimentation.

Applicants' arguments filed 10/2/06 have been fully considered but are not found persuasive.

At page 27-29 of the response, Applicant's position is that the '964 patent does not teach or suggest fusion molecules of the MBP peptide with the IgG heavy chain constant region. The '964 patent does not teach or suggest the administration of an IgG Fc-MBP peptide fusion polypeptide to persons for the treatment of autoimmune disease. The '980 patent allegedly teaches autoantigen such as human myelin basic protein (MBP) and various fragments of MBP such as SEQ ID NO: 18-23 and 16. The reference MBP peptide of SEQ ID NO:18 is allegedly 100% identical to SEQ ID NO:13. The '980 patent does not teach or suggest fusion molecules of the MBP peptide with the IgG heavy chain constant region. The '980 patent does not teach or

suggest the administration of an IgG Fc-MBP peptide fusion polypeptide to persons for the treatment of autoimmune disease. There is no teaching in the '964 patent to combine the MAG protein with the Fc region of IgG. The paragraph at column 7, lines 35 - 45 states "As used herein the term "ligand binding partner" specifically excludes polymorphic and non-polymorphic members of the immunoglobulin gene super family and proteins which are homologous thereto such as ..... myelin associated glycoprotein (MAG)." (emphasis added). MAG is specifically excluded from the described invention. Second, there is no teaching or suggestion in the combination of the reference to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment. While the '980 patent teaches MBP peptides there is no teaching or suggestion to combine the peptide with an IgG Fc region. Thirdly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '964 patent states that "it is an object of this invention to produce ligand binding partners fused to moieties which serve to prolong the in vivo plasma half-life of the ligand binding partner, such as immunoglobulin domains or plasma proteins, and facilitate it purification by protein A. It is a further object to provide novel hybrid immunoglobulin molecules which combine the adhesive and targeting characteristics of a ligand binding partner with immunoglobulin effector functions such as complement binding, cell receptor binding and the like. Yet another object is to provide molecules with novel functionalities such as those described above the therapeutic use, or for use as diagnostic reagents for the in vitro assay of the ligand binding partners or their targets. It is another object to provide multifunctional molecules in which a plurality of ligand binding partners (each of which may be the same or different) are assembled, whereby the molecules become capable of binding and/or activating more than one ligand." The '964 patent provides no motivation to replace the LHR peptide with an MBP peptide in which the MBP serves as an immunogen/tolergen. There is no motivation in the '980 patent to attach the MBP peptide to an IgG heavy region. There is no motivation to generate a fusion protein comprising the MBP peptide. In fact a number of references teach away from the claimed invention. Davidson et al, teaches that two recent phase I clinical trials for treatment of multiple sclerosis by administering altered peptide ligands derived from MBP resulted in either hypersensitivity reactions or exacerbations of multiple sclerosis. Similarly McDevitt indicates that administration of GAD autoantigen epitopes to NOD mice was found to induce immediate hypersensitivity that could lead to death. Accordingly, one would not be motivated to administer MBP to people, much less attach the Fc region to the MBP to increase the half-life of the MBP in the person.

In response to the argument that none of the cited patent teaches administration of an IgG Fc-MBP peptide fusion polypeptide to persons for the treatment of autoimmune disease, it is noted that none of the pending claims recite a method of treating autoimmune disease by administering IgG Fc-MBP peptide fusion polypeptide to persons.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the teachings of the '964 patent pertaining to the fusion polypeptide comprising the constant domain Fc portion of human IgG1, IgG2, IgG3 or IgG4 fused to a second polypeptide such as autoantigen sequence myelin-associated glycoprotein (MAG) for use as pharmaceutical composition for treating autoimmune disease and the teachings of the '980 patent indicating success in isolating the dominant human myelin basic protein (MBP) and various fragments of MBP such as SEQ ID NO: 18-23, and 16 or ENPVVHFFKNIVTPRTP of SEQ ID NO: 18 for a pharmaceutical composition comprising for administration to patients suffering from multiple sclerosis would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

In contrast to applicant's argument that there is no motivation to generate a fusion protein comprising the MBP peptide, the reason or motivation to modify the references may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP 2144.

With respect to the arguments Davidson et al, teaches that two recent phase I clinical trials for treatment of multiple sclerosis by administering altered peptide ligands derived from MBP resulted in either hypersensitivity reactions or exacerbations of multiple sclerosis. Similarly McDevitt indicates that administration of GAD autoantigen epitopes to NOD mice was found to

induce immediate hypersensitivity that could lead to death, it is noted that the claims are not drawn to a method of treating multiple sclerosis. Further, Davidson et al does not teach fusion molecule comprising a first polypeptide sequence comprising at least 85% identity with an IgG heavy chain constant region and a second polypeptide autoantigen comprising at least 90% sequence identity to at least a portion of the amino acid sequence of myelin basic protein (MBP). Likewise, McDevitt does not teach fusion molecule comprising a first polypeptide sequence comprising at least 85% identity with an IgG heavy chain constant region and a second polypeptide autoantigen comprising at least 90% sequence identity to at least a portion of the amino acid sequence of myelin basic protein (MBP).

11. Claims 18-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,116,964 (May 1992; PTO 892) in view of US Pat No 5,858,980 (Jan 1999; PTO 892) as applied to claims 1, 4, 9-14, 16, 22-28, and 40-41 mentioned above and further in view of US Pat No 5,565,335 (of record, Oct 1996; PTO 892).

The combined teachings of the '964 patent, and the '980 patent have been discussed supra.

The claimed invention in claim 18 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 85% identity to amino acid sequence of SEQ ID NO: 3.

The claimed invention in claim 19 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 90% identity to amino acid sequence of SEQ ID NO: 3.

The claimed invention in claim 20 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 95% identity to amino acid sequence of SEQ ID NO: 3.

The '335 patent teach various fusion molecule comprising IgG heavy chain constant region polypeptide having an amino acid sequence at least 97.2% identical to the claimed SEQ ID NO: 3, which is at least 85%, 90%, and 95% identical to the claimed SEQ ID NO: 3 (See reference SEQ ID NO 7, in particular). The reference IgG heavy chain is fused to a second autoantigen polypeptide such as myelin associated glycoprotein (See col. 4, Detailed description, lines 18-31, in particular). The advantage of the Fc in the fusion molecule enhances the plasma

half-life of the fusion molecule (see Summary of invention, col. 5, lines 26-47, Table IV, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the IgG heavy chain constant region (Fc) polypeptide in the fusion molecule comprising a first polypeptide at least 85% identity with an IgG heavy chain fused to myelin basic protein as taught by the '964 patent, and the '980 patent for the human IgG1 Fc having an amino acid sequence at least 97.2% identical to the claimed SEQ ID NO: 3 as taught by the '335 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '335 patent teaches that Fc fusion molecule enhances the plasma half-life of the fusion molecule (see Summary of invention, col. 5, lines 26-47, in particular). The Fc improves the in vivo plasma half-life of the fusion molecule as taught by the '964 patent (see col. 15, lines 19-20, in particular). The '980 patent teaches the immunodominant epitope of myelin basic protein is useful as a pharmaceutical composition for treating patients suffering from multiple sclerosis (see col. 3, lines 45-67, col. 11, lines 20-35 in particular).

Applicants' arguments filed 10/2/06 have been fully considered but are not found persuasive.

At pages 30-31 of the response, Applicant's position is that first, there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment. Secondly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '335 patent teaches CD4 fused with IgG. There is no motivation in the '335 patent to replace the CD4 with an MBP peptide. Finally, none of the references, either alone or in combination provide a reasonable expectation of success from the claimed invention.

Applicant's argument at pages 30-31 of the response has been fully considered but is not deemed persuasive. With respect to the argument with respect to no teaching or suggestion to fuse the heavy chain constant region of the IgG with the autoantigen, the '964 patent teaches a fusion molecule comprising heavy chain constant region of IgG fused to an autoantigen polypeptide such as MAG instead of MBP. However, the '980 patent teaches various MBP fragment as the domain epitope for a pharmaceutical composition would have lead to one of

ordinary skill in the art with the expectation of success in making fusion polypeptide simply by replacing the MAG in the fusion polypeptide as taught by the '964 patent for the MBP as taught by the '980 patent given that both MAG and MBP are autoantigen.

The claimed invention in claim 18 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 85% identity to amino acid sequence of SEQ ID NO: 3.

The claimed invention in claim 19 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 90% identity to amino acid sequence of SEQ ID NO: 3.

The claimed invention in claim 20 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 95% identity to amino acid sequence of SEQ ID NO: 3.

The '335 patent teach various fusion molecule comprising IgG heavy chain constant region polypeptide having an amino acid sequence at least 97.2% identical to the claimed SEQ ID NO: 3, which is at least 85%, 90%, and 95% identical to the claimed SEQ ID NO: 3 (See reference SEQ ID NO 7, in particular). The reference IgG heavy chain is fused to a second autoantigen polypeptide such as myelin associated glycoprotein (See col. 4, Detailed description, lines 18-31, in particular). The advantage of the Fc in the fusion molecule enhances the plasma half-life of the fusion molecule (see Summary of invention, col. 5, lines 26-47, Table IV, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the IgG heavy chain constant region (Fc) polypeptide in the fusion molecule comprising a first polypeptide at least 85% identity with an IgG heavy chain fused to myelin basic protein as taught by the '964 patent, and the '980 patent for the human IgG1 Fc having an amino acid sequence at least 97.2% identical to the claimed SEQ ID NO: 3 as taught by the '335 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One of ordinary skill in the art would have been motivated with the expectation of success in substituting the Fc domain of IgG because the Fc in the fusion molecule enhances the plasma half-life of the fusion molecule as taught by the '335 patent (see Summary of invention, col. 5, lines 26-47, Table IV, in particular).

In contrast to applicant's argument that there is no motivation to generate a fusion protein comprising the MBP peptide, the reason or motivation to modify the references may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP 2144.

12. Claims 29-34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,116,964 (May 1992; PTO 892) in view of US Pat No 5,858,980 (Jan 1999; PTO 892) as applied to claims 1, 4-5, 9-14, 16, 22-28, and 40-41 mentioned above and further in view of Elias et al (of record, J Biol Chem 265(26): 15511-17, September 1990; PTO 892) and Marks et al (of record, J Cell Biol 135(2): 341-354, Oct 1996; PTO 892).

The combined teachings of the '964 patent, and the '980 patent have been discussed supra.

The claimed invention in claim 29 differs from the combined teachings of the references only in that the fusion molecule comprises at least one amino terminal ubiquitination target motif.

The claimed invention in claim 30 differs from the combined teachings of the references only in that the fusion molecule comprises at least one proteasome proteolytic signal, wherein said signal is selected from the group consisting of large hydrophobic amino acid residues, basic amino acid residues, and acidic amino acid residues.

The claimed invention in claim 31 differs from the combined teachings of the references only in that the fusion molecule comprises large hydrophobic amino acid residues, basic residues, and acid amino acid residues.

The claimed invention in claim 32 differs from the combined teachings of the references only in that the fusion molecule comprises at least one endopeptidase recognition motif.

The claimed invention in claim 33 differs from the combined teachings of the references only in that the fusion molecule comprises a plurality of endopeptidase recognition motifs.

The claimed invention in claim 34 differs from the combined teachings of the references only in that the fusion molecule comprises at least one endopeptidase recognition motif selected form the group consisting of cysteine amino acid residue.

Elias et al teach N-terminal residue of the protein is one important structural determinant recognized by ubiquitin ligase and conjugated protein to ubiquitin targets the protein for protein degradation (See page col. 15511, col. 2, second paragraph, in particular). Elias et al teach

protein with hybrophobic amino acid residues such as leucine, or basic amino acid residues such as histidine, arginine and lysine determines the half-life of the protein (See paragraph, bridging page 15511 and 15512, in particular).

Marks et al teach adding ubiquitination target motif such as bulky hydrophobic group di-leucine motif to any protein would target the protein to the lysosome or endosomal compartments for antigen processing to be release from the cell (See abstract, page 348, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to include at least one amino terminal ubiquitination target motif such as large hydrophobic amino acid residue such as leucine as taught by Elias and Marks to the fusion molecule comprising IgG heavy chain constant region fused to a second autoantigen polypeptide of myelin basic protein (MBP) as taught by the '964 patent, and the '980 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Elias et al teach adding hybrophobic amino acid residues such as leucine, or basic amino acid residues such as histidine, arginine and/or lysine to the amino terminal of any protein modulates the half-life of the protein (See page 1552, col. 1, in particular). Marks et al teach adding ubiquitination target motif such as bulky hydrophobic group di-leucine motif to any protein would target the protein to the lysosome or endosomal compartments for antigen processing to be release from the cell (See abstract, page 348, in particular). It is within the purview of one ordinary skill in the art at the time the invention was made to have more than one endopeptidase recognition motifs since it is an obvious variation of the reference teachings of Mark et al.

Applicants' arguments filed 10/2/06 have been fully considered but are not found persuasive.

At page 31-32 of the response, Applicant's position is that the claimed invention is not obvious in light of the combination of the cited references for the following reasons. The '964 patent and the '980 patent have been discussed above. Elias et al. teach that the N terminal residue of the protein is one important structural determinant recognized by ubiquitin ligase to conjugated protein to ubiquitin for protein degradation. Elias et al. teach hydrophobic amino acid residues such as leucine or basic amino acid residues such as histidine, arginine and lysine determine the half-life of the protein. Elias does not teach the elements which are missing from

the '964 patent or the '980 patent. Mark et al. teach that adding ubiquitination target motifs such as bulky hydrophobic group di-leucine motifs to any protein would target the protein to the lysosome or endosomal compartments for antigen processing. Mark does not teach the elements which are missing from the '964 patent or the '980 patent. First, there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment. The '964 patent and the '980 patent do not teach or suggest the fusion of a heavy constant region of the IgG molecule with a myelin basic peptide fragment for the reasons set forth above. The Elias and Marks references do not cure this deficiency. Secondly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '964 patent uses the IgG heavy chain region to increase the plasma half-life of the fusion peptide. It provides no motivation to replace the LHR peptide with an MBP peptide. The Elias and Marks references do not cure this deficiency. Finally, none of the references, either alone or in combination provide a reasonable expectation of success from the claimed invention.

In response to the argument with respect to Elias does not teach the elements which are missing from the '964 patent or the '980 patent, the combined teachings of the '964 patent and the '980 patent have been discussed supra. The claimed invention differs from the combined teachings of the references only in that the fusion molecule comprises at least one amino terminal ubiquitination target motif or at least one proteasome proteolytic signal, wherein said signal is selected from the group consisting of large hydrophobic amino acid residues, basic amino acid residues, and acidic amino acid residues or large hydrophobic amino acid residues, basic residues, and acid amino acid residues or at least one endopeptidase recognition motif such as cysteine amino acid residue.

Elias et al teach N-terminal residue of the protein is one important structural determinant recognized by ubiquitin ligase and conjugated protein to ubiquitin targets the protein for protein degradation (See page col. 15511, col. 2, second paragraph, in particular). Elias et al teach protein with hybrophobic amino acid residues such as leucine, or basic amino acid residues such as histidine, arginine and lysine determines the half-life of the protein (See paragraph, bridging page 15511 and 15512, in particular).

Marks et al teach adding ubiquitination target motif such as bulky hydrophobic group di-leucine motif to any protein would target the protein to the lysosome or endosomal compartments for antigen processing to be release from the cell (See abstract, page 348, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to include at least one amino terminal ubiquitination target motif such as large hydrophobic amino acid residue such as leucine as taught by Elias and Marks to the fusion molecule comprising IgG heavy chain constant region fused to a second autoantigen polypeptide of myelin basic protein (MBP) as taught by the '964 patent, and the '980 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Elias et al teach adding hybrophobic amino acid residues such as leucine, or basic amino acid residues such as histidine, arginine and/or lysine to the amino terminal of any protein modulates the half-life of the protein (See page 1552, col. 1, in particular). Marks et al teach adding ubiquitination target motif such as bulky hydrophobic group di-leucine motif to any protein would target the protein to the lysosome or endosomal compartments for antigen processing to be release from the cell (See abstract, page 348, in particular). It is within the purview of one ordinary skill in the art at the time the invention was made to have more than one endopeptidase recognition motifs since it is an obvious variation of the reference teachings of Mark et al.

With respect to the argument that it provides no motivation to replace the LHR peptide with an MBP peptide, the teachings of the '335 patent is cited for fusing any molecule to IgG heavy chain constant region polypeptide having an amino acid sequence at least 97.2% identical to the claimed SEQ ID NO: 3, which is at least 85%, 90%, and 95% identical to the claimed SEQ ID NO: 3 (See reference SEQ ID NO 7, in particular). The motivation to fuse any antigen to any Fc is that the Fc in the fusion molecule enhances the plasma half-life of the fusion molecule as taught by the '335 patent (see Summary of invention, col. 5, lines 26-47, Table IV, in particular). Even if one does not motive enough to substitute the LHR peptide with an MBP peptide, the teachings of the '964 patent pertaining to the fusion polypeptide comprising the constant domain Fc portion of human IgG1, IgG2, IgG3 or IgG4 fused to a second polypeptide such as autoantigen sequence myelin-associated glycoprotein (MAG) for use as pharmaceutical composition for treating autoimmune disease would have motivate one of ordinary skill in the art to substitute the autoantigen MAG in the fusion molecule as taught by the '964 patent for the autoantigen MBP as taught by the '980 patent for a pharmaceutical composition comprising the fusion molecule comprising Fc fused to MBP for administration to patients suffering from multiple sclerosis. The

strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144. The claimed invention is an obvious variation of the reference teachings.

13. Claims 42-44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,116,964 (May 1992; PTO 892) in view of US Pat No 5,858,980 (Jan 1999; PTO 892) as applied to claims 1, 4-5, 9-14, 16, 22-28, and 40-41 mentioned above and further in view of US Pat No 5,945,294 (of record, Aug 1999, PTO 892).

The combined teachings of the '964 patent, and the '980 patent have been discussed supra.

The claimed invention in claim 42 differs from the combined teachings of the references only in that an article of manufacture comprising a container, a fusion molecule of claim 1 within the container, and a label or package insert on or associated with the container.

The claimed invention in claim 43 differs from the combined teachings of the references only in that an article of manufacture comprising a container, a fusion molecule of claim 9 within the container, and a label or package insert on or associated with the container.

The claimed invention in claim 44 differs from the combined teachings of the references only in that an article of manufacture comprising a container, a fusion molecule of claim 9 within the container, and a label or package insert on or associated with the container wherein the label or package insert comprises instructions for the treatment of an immune disease.

The '294 patent teaches diagnostic kit, which is an article of manufacture (for IgE detection using human Fc epsilon receptor (See abstract, in particular). The kit is useful for diagnosing abnormal conditions in animals that are associated with changing levels of IgE associated with allergy (See column 15, lines 19-23, in particular). A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '294 (See column 14, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the human Fc epsilon receptor in a kit as taught by the '294 patent for the fusion molecule comprising IgG heavy chain constant region fused to a second autoantigen polypeptide of myelin basic protein (MBP) as taught by the '964 patent, and the '980

patent for treating autoimmune disease as taught by the '980 patent. One would have been motivated, with a reasonable expectation of success to do this for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '294 (See column 14, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Claim 44 is included in this rejection because a product is a product, irrespective of its intended use.

Applicants' arguments filed 10/2/06 have been fully considered but are not found persuasive.

At page 33 of the response, Applicant's position is that the '964 patent and the '980 patent have been discussed above. The '294 patent teaches diagnostic kits for IgE detection comprising human Fc epsilon receptor and an allergen. Neither the '964 patent, the '980 patent nor the '294 patent nor a combination of all three teaches or suggests the fusion protein of the IgG Fc region with the MBP peptide in a kit.

In response, the combined teachings of the '964 patent, and the '980 patent have been discussed supra. The invention in claims 42-44 differ from the teachings of the combined reference only in that a kit or an article of manufacture comprising a container, a fusion molecule of claim 1 within the container, and a label or package insert on or associated with the container.

The '294 patent teaches a diagnostic kit, which is an article of manufacture (for IgE detection using human Fc epsilon receptor (See abstract, in particular). The kit is useful for diagnosing abnormal conditions in animals that are associated with changing levels of IgE associated with allergy (See column 15, lines 19-23, in particular). A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '294 (See column 14, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the human Fc epsilon receptor in a kit as taught by the '294 patent for the fusion molecule comprising IgG heavy chain constant region fused to a second autoantigen polypeptide of myelin basic protein (MBP) as taught by the '964 patent, and the '980 patent for treating autoimmune disease as taught by the '980 patent. One would have been motivated, with a reasonable expectation of success to substitute this for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '294 (See

column 14, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Claim 44 is included in this rejection because a product is a product, irrespective of its intended use.

14. Claims 17 and 21 are free of prior art.

15. No claim is allowed.

16. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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